# Appendix 7

## Review of Amendment 32 - Responses to Information Request Dated 15 Nov 2013

**Recommendation:** I reviewed the response in Amendment 32 and they were acceptable. One **PMC** is listed below and a follow-up telecon is scheduled with Bioclon to discuss revising their batch production records to improve documentation of the process performed.

**PMC**

Bioclon commits to performing cleaning validation for the filling equipment. This validation will be completed and the results will be submitted to the application as a PMC-Final Report no later than June 2014.

**Review**

The FDA questions are in **bold** font and Bioclon's responses are in *italicized* font.

a. **Amendment 14 (response to IR dated 21 Jun 2013). Please note that this was Amendment 15.**

**Response to question #7**

**1. In your summary description for the cleaning of the (b) (4) tank used to hold the (b) (4) (b) (4) , which is shipped to Tlalpan for use in manufacture of Anavip, you state that the final rinse of the tank post-cleaning uses (b) (4) . This is not acceptable. The final rinse of the (b) (4) tanks should be with (b) (4) . Please confirm that the final rinse of the tank will be with (b) (4) .**

*Instituto Bioclon Response:*

(b) (4)

**FDA Response**: This response is acceptable.

**2. Please provide the following information:**
**a. clean hold time for the (b) (4) tanks**

*Instituto Bioclon Response:*

*The validity of the cleaning of the tank is* (b) (4) *from the date of cleaning.*

**b. hold time between cleaning and sanitization**

*Instituto Bioclon Response:*
*The hold time between cleaning at Tlalpan and the* (b) (4) *sanitization is up to* (b) (4).

**c. hold time between sanitization and** (b) (4)

*Instituto Bioclon Response:*
(b) (4)

**FDA Response**: The responses to question #2 are acceptable. The (b) (4) is tested (b) (4) times during manufacturing so confirm it still meets (b) (4) standards.

**3. Please clarify what is meant by the terms "sanitizing identification, and verification,** (b) (4) **final rinsing, assembly, identification, verification, validity and registration."**

*Instituto Bioclon Response:*
*The Standard Operating Procedure for the Cleaning and Sanitizing of the Tanks to Transport* (b) (4) *, code P-PB-110, describes the terms:*

(b) (4)

**FDA Response:** This response is acceptable. This clarifies the statement made in the application that was unclear.

Questions 1-3 all were related to the (b) (4) tank used for the transport of (b) (4) from (b) (4) to Tlalpan. The responses given are acceptable and the cleaning of the tank and the transport of the (b) (4) are acceptable. I do not have any further questions or comments.

**Response to question # 8**
**4. For process tank (b) (4) please clarify what product was used to evaluate the cleaning and sanitization of the tank. Please indicate the validated dirty and clean hold times.**

*Instituto Bioclon Response:*
*The product used to evaluate the cleaning and sanitization of the tank was (b) (4) (b) (4) content and they were selected as the worst-case product for the cleaning process validation. The clean hold time is (b) (4) and the dirty hold time is (b) (4).*

**FDA Response:** This response is acceptable. The cleaning validation was performed with the appropriate worst-case product, thus cleaning validation of the tank is acceptable. I do not have any further questions or comments.

**5. The following abbreviations were not defined. Please define the following: (b) (4)**

*The following terms are defined below.*
(b) (4)

**FDA Response:** This response is acceptable. These locations were the location of the (b) (4) samples during the cleaning validation of the tank. These locations are acceptable and the typical locations tested during a validation. All specifications were met. I do not have any further questions.

Question 4 and 5 were related to the manufacturing tank, (b) (4) The tank used during the manufacturing process was appropriately qualified.

b. **Amendment 16 (response to IR dated 17 Jul 2013)**

**Response to question #4**
**1. This response is NOT acceptable. Some type of cleaning validation must be performed on the equipment even if it is dedicated to a specific product. You still must demonstrate effective cleaning procedures since this may have an impact on sterilization of the equipment prior to the next fill due to any residual dirt which may harbor bacteria or shield it from complete steam penetration. Bioclon still needs to have clean and dirty hold**

**times, and hold times post-cleaning prior to sterilization, and sterile hold times for the (b) (4) and other product contact equipment. Please indicate if any type of sampling, such as rinse water sampling, was performed to confirm equipment was clean and any detergents used were fully rinsed away.**

*Instituto Bioclon Response:*
*The cleaning procedures (PNO-PBT-028 "cleaning, sanitizing and operation of the project of vials brand (b) (4) ") are not currently validated. No sampling was performed. Instituto Bioclon will perform the validation of the cleaning procedures for equipment that are involved in the filling of the product and have direct contact with it. The validation process will include clean and dirty hold times, and hold times post-cleaning prior to sterilization, and sterile hold times for the (b) (4) and other product contact equipment. The validation work will be completed within the next 9 months.*

**FDA Response:** This response is acceptable, except for the date of completion. The commitment will be a PMC. **I propose the following for the PMC**:

Bioclon commits to performing cleaning validation for the filling equipment. This validation will be completed and the results will be submitted to the application as a PMC-Final Report no later than June 2014.

**Response to question #9i**
**2. The sterilization time for Load Pattern 1 was (b) (4) . The sterilization time for Load Pattern 2 was (b) (4) . Please provide an explanation for the changes in sterilization times within Load Pattern 1 and Load Pattern 2.**

*The start of the sterilization cycle refers to the time in which all thermocouples temperature is greater than or equal to (b) (4) There are differences between the periods of time because the (b) (4) However, the three runs comply with the pre-established acceptance criteria which are: (b) (4) .*

**FDA Response:** This response is acceptable.

**Response to question #9iii**
**3. A time to reach sterilization temperature was originally requested for each load. This information was not provided. Please provide the requested information.**

*Instituto Bioclon Response:*
*The times to reach sterilization temperature are listed below:*
(b) (4)

(b) (4)

**FDA Response:** This response is acceptable.

**4. The sterilization time listed for Load Pattern 1 is (b) (4) ; however, Load Pattern 1 was validated for a minimum of (b) (4) . Please explain why the sterilization time used for routine sterilization of Load Pattern 1 is less than the time that was validated.**

*Instituto Bioclon Response:*
*During the validation studies,* (b) (4)

**FDA Response:** This response is acceptable and clarifies the seeming discrepancy.

Questions 2, 3 and 4 are related to the autoclave load pattern validation. The responses were acceptable and all load patterns for the autoclave used for the manufacture of Anavip are validated. I do not have any further questions.

**Response to question #16**

**5. After the list for the operation parameters for the crimping machine, there is a note stating,** (b) (4)

**" Please define the term "vensor".**

*Instituto Bioclon Response:*
*This was a typographical error, the correct word is 'vendor'. The sentence should read as follows:* (b) (4)

**FDA Response:** This response is acceptable. I do not have any further questions or comments. The crimping machine is appropriately qualified.

**Response to question #22**

**6. Please define "PW". In one instance in your response it is defined as purified water and in another instance it is defined as potable water.**

*Instituto Bioclon Response:*
*PW means purified water. None of the processes are carried out with potable water.*

**FDA Response:** This response is acceptable.

**Response to question # 25**

**7. I am unable to locate the document "Compress Air Summary for (b) (4) Facility." The link to the document is broken and I am unable to find the document within the documents contained in 3.2.A.1 in the original submission. Please fix the link, provide the exact title of the document, or provide the document.**

*Instituto Bioclon Response:*
*The document is included in section Appendix **3.2A.1 Facility and Equipment; Facilities**: **compress-air-summary-for-(b) (4)-facility***

**FDA Response:** This response is acceptable. Bioclon provided the document requested and I reviewed it and found it to be acceptable. The compressed air that is used (b) (4) specifications. The compressed air is tested for (b) (4) .

**Response for 28ii**
**8. Your response is unclear. You state, "Compressed air is used (b) (4)**

*Instituto Bioclon Response:*
*This was a typographical error; we intended to state that the compressed air is not used for filling or during the freeze-drying process.*

**FDA Response**: This response is acceptable.

c. **Amendment 28 (response to IR dated 07 Oct 2013)**

**Response to question 2a**

**1. The media fill batch product record was translated as requested. I have the following questions about the media fill since the BPR is deficient in the description of the media fill:**
**a. Please indicate if a line stoppage was simulated. If so, how long was the stoppage? Please indicate if your filling SOP, or other applicable SOP, describes the procedure for operators to follow during a line stoppage.**

*Instituto Bioclon Response:*

*Yes, there was* (b)( *line stoppage simulated. Line stoppages were carried out as part of the planned contingencies. The contingencies consisted of:*

- (b) (4)

*The Standard Operating Procedure describing the procedures for an operator to follow in case of line stoppage is presented is the PNO-PBT-010 "Plan of contingency for the Area of filling and lyophilization".*

**b. It is unclear if during a line stoppage or during a change in** (b) (4) **if any vials are removed from the line. Please comment.**

*Instituto Bioclon Response:*
*During the aseptic filling in addition to the aforementioned stoppages (see respond above) one of the contingencies consisted* (b) (4) *Instituto Bioclon will modify the BPR for aseptic filling code: PMP-PBT-002 to be used in the next aseptic filling in March 2014 and include a section indicating that vials exposed to the contingencies* (b) (4)

**c. There is no indication in the BPR when personnel are monitored so I am unable to determine if there was any personnel monitoring. We would expect personnel monitoring, at a minimum, in the following areas: after set up of the filling line, after adding stoppers to the stopper bowl, after any intervention to the fill line such as removing vials or clearing a jammed line. Please indicate when personnel monitoring took place.**

*Instituto Bioclon Response:*
*Currently the personnel are only monitored* (b) (4) *. The plan modification of the BPR for aseptic filling process will* (b) (4) *monitoring of personnel in* (b) (4) *The BPR is being modified and the modified BPR will be used in the next aseptic filling in March 2014.*

**FDA Response:** Bioclon needs to perform a process map and some type of assessment of their process to determine that personnel are monitored at all appropriate steps since the steps listed above are only the minimum steps we expect personnel to be monitored. This was discussed with Bioclon during the 07 Jan 2014 telecon. Bioclon agreed to do this.

**2. The BPR does not capture who sets up the filling machine or capping machine. It also does not capture who adds stoppers to the** (b) (4) **. Please revise your batch record to capture all critical information.**

*Instituto Bioclon Response:*

*The BPR for aseptic filling code: PMP-PBT-002 will be revised to capture who sets up the filling machine and the capping machine and who adds stoppers to the* (b) (4) *. The BPR is being modified and the modified BPR will be used in the next aseptic filling in March 2014.*

**FDA Response:** This response is acceptable. The BPR revision was discussed with Bioclon during the 07 Jan 2014 telecon. Bioclon agreed to do this.

**3. Please provide the sterile hold times for** (b) (4) **. Please indicate if these times were challenged during the media fill.**

*Instituto Bioclon Response:*
*The sterile hold time for the* (b) (4) *. These times were used in the aseptic filling process but not challenged; however for the next aseptic filling in March 2014 these times will be challenged.*

**FDA Response:** This response is acceptable; however Bioclon has challenged the (b) (4) maximum hold time since this is how long the sterilized (b) (4) are held prior to use in the media fill. No further challenge is needed. This was conveyed to Bioclon during the 07 Jan 2014 telecon.

**4. Please indicate if** (b) (4) **of bulk drug substance can be used for the filling of a lot. If so, was this simulated during the media fill?**

*Instituto Bioclon Response:*
*Yes,* (b) (4) *of bulk drug substance can be used for the filling of a lot. Yes, it was simulated and so, during the aseptic filling* (b) (4) *were used and taken as the worse case.*

**FDA Response:** This response is acceptable; however none of this information was captured in the BPR. The need to capture critical information such as number of (b) (4) used for filling was discussed with Bioclon during the 07 Jan 2014 telecon.

**Response to question 2b**

**5. The results for personnel monitoring of the** (b) (4) **filling operators were provided as requested; however, there is no indication of when the monitoring occurred since it is not captured in the BPR. Please indicate when the personnel monitoring occurred during the media fill.**

*Instituto Bioclon Response:*
*The monitoring of the personnel was carried out during aseptic filling at* (b) (4) *of the filling. The BPR is being modified to record the steps when the monitoring of the*

*personnel occurs and the modified BPR will be used in the next aseptic filling in March 2014. Instituto Bioclon, S.A de C.V. Confidential Sequence* (b) (4) *– BL 125488/0*

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|---|
| **FDA Response**: This response is acceptable. All personnel monitoring was acceptable. The need to record personnel monitoring in the BPR was discussed with Bioclon during the 07 Jan 2014 telecon. |

d. **Amendment 29 (response to IR dated 17 Oct 2013)**

**Response to question #2**

**1. In your response, you indicated that the acceptance criteria are based on statistical analysis of batches of** (b) (4) **manufactured during the years of 2005-2009 and** (b) (4) **manufactured (2009-2012). The specifications are only the preliminary specifications set until you have manufactured at least** (b) (4) **lots of Anavip in the** (b) (4) **and then the specifications will be subject to review. The specifications were set for the vials that are filled in the Tlalpan facility which is a** (b) (4) **fill and** (b) (4) **crimping process. The process in the** (b) (4) **facility is an** (b) (4) **fill and crimp capping process. Please indicate if an AQL sampling for visual inspection is being performed for the final container (vial) after the 100% visual inspection and prior to release? If so, what are your sample size and acceptance limits?**

*Instituto Bioclon Response:*
*According to the instructions outlined in the SOP PNO-INS-003 for Visual Inspection of the* (b) (4) *Products, after the visual inspection by the quality assurance chemist, production must perform the inspection of containers following the* (b) (4) *standard. The selection of the number of samples will depend on the size of batch using the general inspection II standard.*

*The AQL sampling for visual inspection for the final container are dependent upon the classification and defect of the final containers after the 100% visual inspection. The vials are inspected during the packaging process as well. Table 1 below lists the classification, defect and AQL for the Anavip sampling process.*

*Table 1 - Classification, Defect and AQL for the Anavip sampling process*

| ***Defect Classification*** | ***Type of Defect*** | ***Defect*** | ***AQL*** |
|---|---|---|---|
| *Critical* | (b) (4) | | |

| | |
|---|---|
| | (b) (4) |
| *Major* | |
| *Minor* | |

**FDA Response:** This response is acceptable. I have no further questions or comments. The visual inspection of the vials is acceptable.